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Review

Re-irradiation for head and neck squamous cell carcinoma

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KEYWORDS

Squamous cell carcinoma;
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Abstract *Introduction:* Local recurrences after curative treatment have a potential for cure with salvage surgery or with re-irradiation.
Methods: We reviewed the PubMed for articles published in English with key words squamous cell carcinoma, recurrent, re-irradiation, prognostic factors to find relevant articles describing prognostic factors, re-irradiation, and outcome for recurrent head and neck squamous cell carcinoma.
Results: Various factors including age, performance status, time for recurrence, previous radiation dose volume and site of recurrence, previous use of chemotherapy are all prognostic factors in recurrent head and neck squamous cell carcinoma. Surgery is feasible in very select subgroup of patients and must be done when feasible. Re-irradiation with the aid of modern sophisticated technology is safe and confers durable and clinically meaningful survival benefit. Re-irradiation in head and neck recurrent squamous cell carcinoma may provide an expected median survival of 10–12 months. Chemotherapy may be added along with radiation in the recurrent setting.
Conclusion: Treatment approaches may have to be personalized. Re surgery must be done in all patients in whom it is feasible. In patients in whom surgery is not feasible, re-irradiation must be evaluated as a therapeutic option especially in patients with limited volume recurrence.

Contents

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer globally [1]. The advances in surgical and radiotherapy techniques have contributed tremendously toward improved outcome with less morbidity in these patients [2]. Despite the advances in the last two decades, 35–40% of patients recurs locally or loco-regionally and poses a significant health burden. Second primary cancers in the head and cancer region further add to this burden, which can be as high as 20–25% in a long term [3]. The treatment of recurrent/second primary HNSCC is always challenging and is associated with significant morbidity [4]. A balance has to be achieved between local control and treatment related morbidity and mortality. Salvage surgery alone has yielded dismal results as has systemic chemotherapy alone [4,5–8]. Median survival with both these approaches has ranged from 5 to 9 months. In addition, many patients are found unsuitable for surgery because of disease extent or morbidity associated with such approach. Re-irradiation of such cases has been tried in the recent practice with promising results. Understanding of the molecular biology and genetic aberrations has paved for newer targeted drugs and are being increasingly tried for the treatment of such cases. However, there is limited prospective data about the management of recurrent/second primary HNSCC (rHNSCC). Hence, management of these tumors varies widely across institutes and based on local perception, available resource. The non-availability of prospective data also precludes comparing one modality to the other and finds the optimum based treatment option. In this review we intend to look into current status of re-irradiation for the treatment of recurrent/second primary HNSCC (rHNSCC).

Search methodology

We performed a comprehensive search of the PubMed, SCOPUS and Google Scholar with the following MesH terms: "reirradiation in head and neck cancer, radiation in recurrent head and neck cancer, reirradiation AND recurrent head and neck cancer AND treatment, survival" to find all possible publications pertaining to rHNSCC. We also conducted a detail search of the references in the available article to retrieve missing articles and conducted a hand search in Google to find any possible publication. After a thorough search the duplicates were removed and the remaining articles were looked into detail.

Investigations

As patients with local or nodal recurrence would undergo a salvage surgery or salvage re-irradiation it is important to rule out any other site of disease that is not evident clinically. An indirect laryngoscopy and upper gastrointestinal endoscopy must be done in all patients and suspected abnormal areas must be biopsied. A contrast enhanced magnetic resonance imaging (MRI) of the head and neck may be superior to contrast enhanced computed tomography (CT) depending on the tumor subsite and tumor extensions. Soft tissue delineation of the disease may be better appreciated in an MRI than a CT. In addition the perfusion and diffusion-weighted MRI helps in differentiating recurrent cancer from post radiation changes [9]. PET scan also is of great help in this scenario and is associated with a high predictive value in patients with recurrence post chemoradiation [10].

The need for a re-biopsy is sometimes debated in a recurrent head and neck cancer patient. It may be avoided in some patients in whom recurrence occurred early and have a diffuse metastatic disease that is clinically correlating with the natural course of the disease. This is particularly important in these patients due to the field cancerization phenomenon that occurs in head and neck cancers [11]. It is also of significance as the patient might have developed a radiation induced second primary which is usually a sarcoma, which should be salvaged surgically [12,13].

Prognostic factors in recurrent Head and neck squamous cell carcinoma

Prognosis with salvage treatment depends on disease related factors or treatment related factors. Balancing toxicity and disease control becomes an important issue in re-irradiation. Disease related factors are site of recurrence, previous response

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to radiation therapy, time from previous radiation and human papilloma virus (HPV) status [5,6]. Treatment related factors include usage of conformal radiation therapy, dose of reirradiation, concurrent chemotherapy usage, salvage surgery and radiation volume [7,8,14]. Patient related factors include age, performance status, comorbidities, organ dysfunction from previous treatment, feeding tube dependency, tracheostomy and soft tissue defect [15–18].

Tanvetyanon et al. in a retrospective series of 103 patients found comorbidity and organ dysfunction as independent predictors of survival. Reasons attributed were both factors may lead to suboptimal cancer directed therapy and increase risk of death from cancer related causes and may cause death due to non-cancer related causes as well. Other factors that had prognostic implications were T stage, tumor bulk, re-irradiation dose, time interval between previous radiation and current. [19]. In a similar series of 79 patients aged less than 50 years, a disease free interval of two years or more positively influenced survival [20]. Choe et al. evaluated phase 1 and phase 2 protocols of 166 patients who underwent chemo radiation in recurrence. Prognostic factors for overall survival were previous chemoradiotherapy (CTRT), surgery before CTRT, re-irradiation and RT interval. Patient who had previously received CTRT had dismal outcomes. Reason attributed was aggressive tumor biology and resistant clonogens [21].

General treatment approach

Various available treatment options should be discussed with the patients with particular emphasis of treatment outcome and toxicity. Surgical salvage should be attempted whenever possible as surgical salvage in recurrent setting has been found to be an independent prognostic factor [4]. The patients must be evaluated with special consideration to factors like performance status, age of the patient, site of recurrence, volume of recurrence, disease free interval, and presence of severe co-morbidity. The sub-sites like oral cavity and limited nodal recurrence are ideal candidates for a surgical salvage. Specific issues related to surgery in recurrent setting like wound healing, organ dysfunction, dependency on feeding tube and increased blood loss during surgery must also be kept in mind before taking a patient for salvage surgery. Post radiation fibrosis in the neck also makes surgical salvage difficult in some cases.

The availability of modern surgical techniques like trans-oral robotic surgery (TORS), trans-oral microsurgical approaches have made surgery a viable option in oropharyngeal cancers with small disease volume. Those patients who are found not suitable for surgery may be evaluated for re-irradiation. But here also careful patient selection is the key to optimize outcomes. Those who are not suitable for either may be given systemic chemotherapy with a palliative intent. A treatment approach to a patient with localized recurrent HNSCC is given in Fig. 1.

Re-irradiation in recurrent/second head and neck cancers

Re-irradiation has long remained an unpopular treatment option because of variety of reason including fear of excessive toxicity, unpredictable dose delivery beyond the normal tissue tolerance and non-availability of imaging modality. With advent of sophisticated radiotherapy techniques like stereotactic radiotherapy, image guided radiotherapy and intensity modulated radiotherapy, re-irradiation rHNSCC has gained momentum. Re-irradiation alone or in combination with chemotherapy can be offered in patients not suitable for surgery. In addition, reirradiation can also be offered for patients

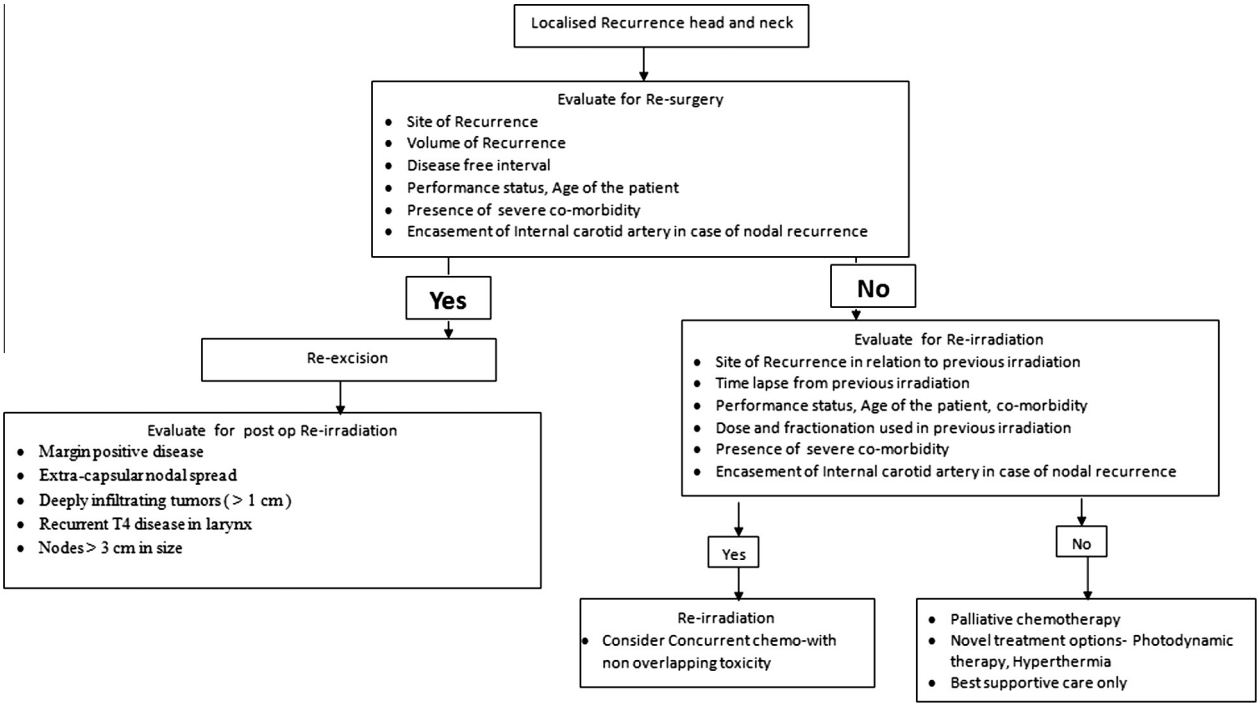

Figure 1 Proposed treatment approach for a recurrent head and neck cancer.

with adverse pathologic feature after salvage surgery. In the subsequent segments we will discuss about patient selection criteria for re-irradiation, the acceptable dose fractionations, role of brachytherapy, target volume definitions, the role of concurrent chemotherapy, toxicity prediction, prevention, mitigation and treatment of radiation toxicity.

Patient selection criteria for re-irradiation

There are a number of patient related, tumors related and previous treatment related factors that predict prognosis after re-irradiation. Charlson co-morbidity index, ACE grading – 27 [19], feeding tube dependency, presence of tracheostomy, presence of skin necrosis, Karnofsky performance status (KPS) and age [22] are patient related factors that define prognosis and help in selecting patients for re-irradiation.

Smaller tumor volume(<221 ml), nasopharyngeal and laryngeal recurrence, longer time interval of recurrence (>16 months) are some of the tumor related factors that predict favorable prognosis compared to patients with larger volume, non-laryngeal primary, and early recurrence [20,22]. Patients treated with conformal techniques and for smaller volumes in initial treatment are expected to fare better with lesser toxicity compared to conventional treatment [20,22]. Patients treated with conformal techniques and for smaller volumes in initial treatment are expected to fare better with lesser toxicity compared to patients treated with conventional technique. Patients who received chemotherapy as part of initial treatment are associated with increased toxicity [21]. Not many molecular factors have been validated for selecting patients for re-irradiation. While treating patients with hypofractionated radiation, the risk of carotid blow out should be considered. Only patients with <180 degree encasement of carotid artery on imaging and absence of ulceration can be taken up [23]. A carotid blow-out syndrome (CBOS) index has been constructed by a retrospective analysis of cases receiving hypofractionated RT to help select patients.

In the post-operative setting patients with margin positive disease, extracapsular nodal spread, deeply infiltrating tumors (>1 cm), rT4 disease in larynx and nodes >3 cm in size are to be considered for re-irradiation [24,25]. Point should be made that the indications of postoperative re-irradiation are less discussed. Janot et al. did not include patients with R1 resection. However, from all other series it appears that re-irradiation should be delivered for margin positive resection and ECE. Rest of the factors should play an important role to tradeoff between toxicity and benefit of re-irradiation.

Dose fractionations for re-irradiation

Dose fractionation is critical in eradiating the tumor cells. There are different radiation schedules-hyper fractionation, accelerated fractionation and hypo fractionation. Radiation in hyper fractionation is delivered in small dose per fraction with two or three fractions delivered every day to achieve a higher biologically effective dose to the tumor when the α/β ratio for tumor cells is greater than that for the dose-limiting, late-responding normal tissue. Hyper fractionation also induces radio-sensitization through cell-cycle redistribution, whereas, accelerated radiation aims to complete the scheduled radiation before the accelerated repopulation kicks off following a lag phase of nearly 4 weeks. An incremental dose of 0.6 Gy is required after this to counter the accelerated repopulation to achieve tumor control. Based on these principles, hyper fractionation would be the preferred approach for re-irradiation because of improved sparing of late responding tissues with equal total dose. There is a considerable debate regarding the optimal dose fractionation in re-irradiation. A dose of >72 Gy biological equivalent dose (BED) or equivalent dose 2 Gy (EQD2) of 60 Gy has been shown to have favorable OS in certain series compared to less than 72 Gy [22]. The incidence of carotid blowout was higher when 1.5 Gy twice daily fractionation five days a week on alternate weeks or delayed accelerated hyper fractionation was used compared to 2 Gy daily or 1.2 Gy twice daily five days a week [26]. Hypo-fractionation 48 Gy BED in five fractions has provided comparable results in terms of PFS and OS in a small series but with increased late toxicity. Certain criteria like CBOS index have been created to define suitable patients for hypo fractionation [23]. So the most acceptable and effective dose fractionation seems to be 60 Gy in 30 fractions over six weeks or 64 Gy in 54 fractions twice daily over 5.5 weeks. The final dose prescribed must also take into account the technique used, volume of recurrence, dose received by vital structures during previous irradiation. Hypo-fractionation can be considered with the caveat of increased risk of late toxicity. Hypo-fractionation is useful in small volume recurrence far from the spinal cord and carotids.

Target volume definition for re-irradiation

After radiation and surgery, normal lymphatic flow gets disrupted. So, in recurrent tumors of head and neck lymph node metastases do not follow the expected pattern based on location and size of primary. Lymphoscintigraphy studies have shown that in around two thirds of cases the lymph flow is altered post-radiation [27]. Irradiating uninvolved nodal region leads to increased volume of irradiation and higher toxicity. Recurrence can occur only in primary, only in nodes or in both nodes and primary. If recurrence is only in the primary, the target volume is defined as gross tumor plus a 0.5–1 cm margin to form clinical target volume (CTV). If only in nodes, the target volume will include the involved nodal level or in few cases only the gross node with a 0.5–1 cm margin [20]. The need to use a margin to account for microscopic disease has been questioned as most recurrences that have occurred after re-irradiation have been in field recurrences [28].

The target delineation should include the use of imaging modalities of MRI and PET. PET integration in planning has demonstrated to shift the location of GTV when compared to CT alone because of clearer differentiation with fibrosis and post treatment changes [29,30]. MRI will help in identifying fibrosis and identifying carotid vessel ulceration and encasement. It is difficult to comment on volumes to be treated when both primary and nodes are involved and should be left to the physician's discretion. The re-recurrence is most commonly seen in the areas of initial GTV. Hence, elective local or nodal irradiation is not beneficial [20].

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Technique for re-irradiation

As re-irradiation may be associated with higher toxicity, more so with concurrent chemotherapy it is advisable to use the best conformal technique. Compared to conventional technique intensity modulated radiotherapy (IMRT) enables delivery of conformal dose to the target, but at the risk of increased integral dose. Lee et al. reported higher loco regional failure with non-intensity modulated techniques [8]. The use of image guidance during radiation delivery help in reducing the margins given for the planning target volume and thus must be used. Proton therapy also needs to be evaluated due to its physical property of the Bragg peak. Point should be made that proton therapy is not necessarily superior in all patients [31]. But, for eligible patients proton therapy may impart long term disease control. Hayashi et al. in a series of 34 patients combined intra-arterial chemotherapy with proton therapy. They reported encouraging 1-year and 2-year LC rates of 77% and 60% [32]. In another recent report Romesser et al. reported limited toxicity with proton beam reirradiation. The authors reported acute grade 3 or greater toxicity in the form of mucositis (9.9%), dysphagia (9.1%), esophagitis (9.1%), and dermatitis (3.3%) [33]. Thus the best conformal technique available must be used for re-irradiation with the use of image guidance.

Dose constrains for the organs at risk

There is paucity of data regarding optimum dose constraints for re-irradiation. So, whenever dose constraints are discussed it is based on some retrospective literature only discussing toxicity profile for a given set of patients. Dose constrains for re-irradiation must be individualized on a case to case basis depending on the previous dose fractionation used, and time since previous irradiation. In a study by Zwiker et al. the risk for xerostomia was significantly higher for cumulative mean doses of $\geqslant$45 Gy to parotid glands [34]. Spinal cord is one of the most critical organs at risk during radiation. As these patients already have radiation up to 70 Gy the spinal cord receives up to the maximum tolerable dose by then and limits the further option of dose delivery. In this context Schultheiss et al. made an import revelation that after an initial dose of 45 Gy, 50% recovery happens for an elapsed period of two years [35]. Nieder et al. in a literature review found small risk of myelopathy after $\leqslant$135.5 Gy [BED] when the interval is not shorter than 6 months and the dose of each course is $\leqslant$98 Gy [36]. Sminia et al. also shared similar view of spinal cord recovery after primary radiation and cumulative irradiation dose applied to the spinal cord can vary between 125 and 172% of the BED tolerance [37]. They also found that keeping cumulative maximum dose to the spinal cord of 53 Gy and 63 Gy to the brain stem is safe in patients with re-irradiation. Similarly a study by Yamasaki et al. had found that re-irradiation dose to spinal cord and brainstem, below 60 Gy was safe without any long term neurological complications [28]. The cumulative mandible below 70 Gy, and two-thirds laryngeal dose below 50 Gy may be safe [38]. Chua et al. in a phase II study for recurrent nasopharyngeal carcinoma used the following dose constraints: 10 Gy $\leqslant$ 10% for brainstem, 4 Gy $\leqslant$ 5% for spinal cord, 8 Gy $\leqslant$ 5% for optic nerve and chiasm, 10 Gy $\leqslant$ 5% for orbit, and 10 Gy $\leqslant$ 10% for temporal lobe. The authors reported modest late toxicity with these dose constraints of 7% and 25% grade III toxicity at 6 and 12 months [39]. But the final dose constrain for an IMRT must be personalized on a patient to patient basis.

Brachytherapy for re-irradiation

Brachytherapy allows for a very conformal radiation if recurrence is confined to primary or single lymph node. But performing brachytherapy may be difficult in a re-irradiation setting. Fibrosis of neck may make placement of needles difficult. Often the location of recurrence like larynx and hypopharynx is inaccessible to brachytherapy. Trismus due to prior radiation and disease per se makes placement of needles difficult in anterior and base of tongue. If recurrence is close to bones like mandible, the high dose per fraction and dose rate in HDR brachytherapy may lead to osteoradionecrosis. The risks may thus outweigh the benefits of the procedure in a patient who has limited survival.

There are very few studies that have used brachytherapy in a reirradiation setting. In a phase I/II reirradiation study by Martinez–Monge et al. 25 patients were treated with perioperative high dose rate brachytherapy (4 Gy twice daily $\times$ 8 (32 Gy) for R0 resections and 4 Gy twice daily $\times$ 10 (40 Gy) for R1 resections) [40]. The authors reported a 4 year local control rate of 85.6% and OS of 46.4%. However 40% (n = 10) developed RTOG grade 3 or higher toxicity. Strnad et al. evaluated pulsed dose rate brachytherapy with chemotherapy or hyperthermia for rHNSCC [41]. The authors reported improved local control when PDR brachytherapy was used in combination with systemic chemotherapy.

Post-operative reirradiation

Re-irradiation after salvage surgery is required for patients with adverse pathological features. Indications for reirradiation after salvage surgery are extra nodal spread, positive surgical margins, and/or other risk factors like close margin, lymphovascular space invasion [24,42]. Kasperts et al. in a prospective study of 39 patients reported 3 year loco regional control and overall survival 74%, 44%respectively, however at the cost of higher toxicity [42]. Janot et al. randomly assigned 130 patients with head and neck cancer treated with salvage surgery to full-dose reirradiation combined with chemotherapy or to observation. The authors reported significantly improved disease free survival but OS was not different between two arms. The authors also report higher rate of treatment related toxicity. Unfortunately, the authors do not mention about techniques of radiation. Radiation technique would be of importance in such cases for limiting the toxicity. Interestingly, 37% patients in the reirradiation arm had $\geqslant$3 node positive compared to 12% in the observation arm. It appears such high risk patients may have contributed to larger volume of radiation and death secondary to toxicity [24].

Systemic therapy with re-irradiation – feasibility and outcomes

A number of systemic agents like paclitaxel, carboplatin, docetaxel, erlotinib, cisplatin, hydroxyurea and adenoviral vector expressing TNF alpha have been integrated with re- irradiation [42–48]. The logic is to eradicate microscopic disease that

may be left out as the irradiation is to a limited region and also to act as a radio sensitizer. The use of chemotherapy has not prolonged survival significantly in many series of reirradiation. A large number of patients receiving re-irradiation would have also received chemotherapy either concurrently or in the neoadjuvant setting for the primary disease. The use of chemotherapy in the primary setting may have led to resistance by increased efflux of drugs by tumor cells, improved DNA repair mechanisms and increased glutathione production (GSH). All these may contribute to decreased effectiveness of chemotherapy along with radiation in the recurrent setting. Also drugs like cisplatin may also lead to cumulative toxicity mainly the neuropathy. The specific issue whether addition of chemotherapy adds to survival in patients undergoing re-irradiation for head and neck cancer is not well addressed in studies. But, it would be logical to use a chemotherapy which has a different mechanism of action and minimal cross resistance with the drug used in the primary disease while treating recurrent disease. A summary of various chemo-re-irradiation trials are summarized in Table 2 [25,42–47].

Toxicity with re-irradiation

Toxicity is one of the main concerns during re-irradiation for a recurrent HNSCC. Acute mucositis is the predominant adverse reaction during radiation which may be more severe with addition of chemotherapy. This can be reduced to a great extent using more conformal techniques for re-irradiation thus reducing the amount of mucosa coming in the radiation field. Usually the acute mucositis subsides and is manageable. But what is more worrisome is the late toxicity. The late toxicity ranges from the dreaded carotid blow out to the chronic xerostomia. In our experience 30% patients suffered from acute grade 3 or worse toxicity. In our series 7 patients suffered from grade 3 skin toxicity, 12 patients suffered from grade 3 mucosal toxicity, and 5 patients had grade 3 laryngitis. However, there was no death because of toxicity or carotid blow out. However, point should be made nearly 50% patients receive re-irradiation by conventional technique [20].

The incidence of carotid blow out may be as high as 5% [6]. This is a life threatening complication and can be avoided to a great extent by careful patient selection and selecting suitable fractionation schedules. Similarly the incidence of osteoradionecrosis has ranged in literature from 8% to 11% [5,6]. Other severe toxicities associated may be mucosal necrosis, chronic xerostomia, brachial plexopathy, subcutaneous fibrosis and hypothyroidism. Accelerated carotid artery stenosis, and increased incidence of second malignancy may be seen in such cases. Hoebers et al. in a retrospective data of 58 reported 43% serious (late) toxicity $\geqslant$Grade 3. This categorically points to the fact that a delicate balance between effectiveness and toxicity is required for the practice of reirradiation [49]. However, we must emphasize that most of the literature present limited absolute data which must be considered a limitation compared to actuarial rate and perhaps underestimate the true incidence of toxicity. A summary of various trials that have evaluated re-irradiation in recurrent head and neck cancers is given in Table 1.

Table 1 Summary of various trials that have evaluated re-irradiation in recurrent head and neck cancers.

Trial	Technique of radiotherapy	RT dose median	Survival outcomes	Toxicity
Salama et al. (2006) $n = 115$ [6]	Conventional or 3D conformal	64.8 Gy	Median overall survival 11 months	Grade 4 or higher • Osteoradionecrosis-11.3% • Carotid hemorrhage 5.2%
Lee et al. (2007) $n = 105$ [8]	Intensity modulated radiation therapy-70%	59.4 Gy	2-year loco-regional progression-free survival-42% 2-year overall survival-37%	Acute grade 3-4 toxicity-23% Late grade 3-4 -15%
Sulman et al. (2009) $n = 105$ [14]	Intensity modulated radiation therapy	60 Gy	2-year loco-regional control-64% 2-year overall survival-58%	Severe toxicity 20%
Mallick et al. (2014) $n = 79$ [20]	Conventional-46.8% 3D conformal-43.3% Intensity modulated radiotherapy-7.6%	45 Gy	Median progression-free survival-15.0 months	Acute Grade III toxicity 30%
Janot et al. (2008) $n = 130$ [65 patients received re-irradiation] [24]	Conventional or 3D conformal	60 Gy	Significantly better DFS, LRC favoring RT arm. However, OS was not different between two arms	Grade 3 or 4 acute toxicity-28% Grade 3 or 4 late toxicity-39%
Popovtzer et al. (2009) $n = 66$ [28]	Intensity modulated radiation therapy or 3D conformal	68 Gy	Overall survival at 2 years 40%	Grade 3 or higher late toxicity-29%
De Crevoisier et al. (1999) $n = 169$ [5]	Conventional	60 Gy	Median overall survival 10 months	Acute Grade III mucositis-30% Neck fibrosis-41% Mucosal necrosis-21% Osteoradionecrosis-8% Trismus-30%.

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Table 2 Summary of various trials that have used concurrent chemotherapy in Re-irradiation setting.

Trial	Phase of trial	RT Dose and concurrent chemotherapy	Survival outcome	Toxicity
Lartigau et al. (2013) [43]	Phase II trial	Re-irradiation of 36 Gy in six fractions by SBRT with five doses of cetuximab	1 year OS = 47.5% (95% CI = 30–62%)	One toxic death by hemorrhage
Kharofa et al. (2012) [44]	Phase II trial	Re-irradiation to median dose 60 Gy at 2 Gray per fraction with concurrent weekly Paclitaxel and carboplatin	Median OS = 16 months 5 year survival = 20%	Grade 3 neutropenia = 15% Gastrostomy tube need = 68% Osteoradionecrosis 3 patients
Berger et al. (2010) [45]	Phase II trial	Re-irradiation 40 Gy split course alternating with 3 cycles Docetaxel and Cisplatin	Median OS = 13.4 months	Severe late toxicity in 33% patients
Rusthoven et al. (2010) [46]	Phase I trial	Dose escalation trial for concurrent and maintenance Erlotinib Re-irradiation 66 Gy in 2.2 Gy fraction with concurrent and maintenance Erlotinib of 150 mg daily feasible	Median follow-up was 8.4 months overall and 15.1 months for surviving patients	Acute Grade 3 toxicity in 69% One patient had Grade 5 carotid hemorrhage
Iseli et al. 2009 [25]	Phase II trial	Postoperative re-irradiation with concurrent Cisplatin	Median OS = 12.5 months	Functional outcomes declined with addition of chemotherapy
Siewert et al. (2013) [47]	Phase I trial	Dose escalation study of replication deficient adenoviral vector expressing TNF alpha with 5 FU, Hydroxyurea and radiation	Median OS = 9.6 months	Monitoring for thrombotic events necessary but integration feasible

Expected outcome with re-irradiation in head and neck cancers

The median overall survival expected from re-irradiation may vary from 10 to 12 month, with a 2 year overall survival ranging from 37% to 58% in various reported trials [6,8,14]. The overall survival may be slightly higher for patients who underwent re-irradiation in the postoperative setting with a range of 12–16 months [25,34,35]. The 2 year local control that may be expected from re-irradiation may be in the range 40–64% [8,14]. Thus a good survival can be achieved along with good local control in selected patients of head and neck cancer treated with re-irradiation.

Conclusion

The recurrent head and neck cancer has always been considered a poor prognostic subgroup. Little effort has been made to look into these patients separately. Hence, the treatment of these cases has always been made with a palliative intent and salvage with curative option has rarely been made especially those with limited volume recurrence occurring after a long disease free interval. In patients with local recurrence or loco-regional recurrence surgery should be attempted for best cure. In cases with high risk feature (margin positive/Extra capsular extension) consolidation should be done with postoperative re-irradiation alone or with chemotherapy. Patients deemed inoperable/unresectable should be considered for re-irradiation alone or with concurrent chemotherapy with an expected median survival of 10–12 months.

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